REMARKS

Reconsideration of this application is respectfully requested. Claims 1 and 38 have been amended. Claims 18-21, 27 and 39 have been cancelled. With these amendments, claims 1, 4-7, 11-15, 22, 24-26, 28-30, 32-36, and 38 are currently pending in this application. These amendments are made without prejudice or disclaimer and do not add any new matter. Applicants retain the right to prosecute any cancelled or otherwise unclaimed subject matter in a continuing, divisional or other application as appropriate. Consideration and entry of this reply is respectfully requested.

Amendments to the claims

The claims have been amended to more clearly reflect Applicants' claimed subject matter. Claim 1 has been amended to require at least two steps, namely:

(a) administering to a mammal having metastatic melanoma a composition comprising a recombinant virus encoding a melanoma-associated tumor antigen along with at least one peptide comprising an epitope of the tumor antigen such that the mammal develops a T-cell immune response against the tumor antigen; and,

(b) subsequently administering at least 10 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal for four weeks, wherein the IFN-α2b is initially administered between 1.5 and 17 months after step (a) provided there is no evidence of T cells reactive against the tumor antigen in the mammal as measured by flow cytometric assay or ELISPOT assay,

wherein, following steps (a) and (b), the mammal has no evidence of metastatic disease.

Amended claim 1 finds support in the originally-filed specification. For instance, step (a) finds support at paragraph [0082] which describes initial "injections of the ALVAC(2)-gp100M recombinant virus...along with the two modified peptide epitopes...." And paragraph [0092] explains that "if patients had not achieved a measurable anti-gp100 response to vaccination, treatment wit HDI did not lead to a measurable increase in gp100-reactive T cells."

Regarding step (b), paragraph [0083] describes high-dose interferon (HDI) treatment as consisting of "20 MU/m^2/d IV 5 days/week x 4 weeks." And paragraph [0092] states:

> None of the patients had evidence of circulating gp100-reactive T cells by any of these two assays before beginning the month of HDI (FIGS. 1a and b, "Follow-up" dot-plots; FIG. 3b; FIG. 5b; and data not shown).

Similarly, paragraph [0094] states that patient M166, "[a]t the end of the vaccination period, the frequency of gp100-reactive T cells fells (FIG. 3A) and disappeared by the time that HDI was instituted (FIG. 1a, 'Follow-up' dot-plot; FIG. 3b)." And paragraph [0096] explained that patient "M335 transiently responded to vaccination, as measured by tetramers and ELISPOT assays, but this response was lost by the time that HDI was instituted (FIG. 1b, FIG. 5)."

Regarding evidence of metastatic disease after steps (a) and (b), paragraph [0093] explains that the treatment caused a metastatic mass to disappear in patient M166. And paragraph [0095] explains that the treatment caused metastases in the chest wall, axilla, and lung to "disappear". Thus, these amendments do not add any new matter.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 38 and 39 stand rejected under 35 U.S.C. § 112, first paragraph, as containing new matter. Claim 39 has been cancelled; the rejection of this claim is therefore moot. The Office Action alleged that "the specification does not provide any description of what is/are the 'evidence of melanoma progression' following step (b) to be identified by radiological examination." For example, paragraph [0095] describes the treatment and assessment of patient M335. As described therein:

> Six weeks after the last vaccine injection, she was started on HDI. Within 2 weeks, the palpable masses in the chest wall and left axilla had disappeared, as confirmed by the CT scan taken 2 months after completing HDI (Fig. 4c). Radiologic evidence of lung metastases (FIG. 4e) also disappeared (FIG. 4f).

Applicants respectfully maintain that one of ordinary skill in the art would understand "radiological examination" to include, for example, standard radiographic technology such as CT scan. Thus, the specification clearly explains that the assessment of "radiologic evidence of metastases" was carried out after treating patients using the method of claim 1. And, as explained on p. 27 of the Office Action, "identification of evidence of melanoma progression by radiological examination was known in the art." Accordingly, claim 38 does not include any new matter. Withdrawal of these rejections is therefore respectfully requested.

Rejections under 35 U.S.C. § 103(a)

A. Rejection of claims 1, 4-7, 11-15, 18-22, 28-30, 32-35, and 37-39 as obvious over Paoletti in view of Emtage, Kirkwood, and Morton

Claims 1, 4-7, 11, 12, 14, 15, 18-23 and 28-34 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Paoletti (U.S. Pat. No. 5,942,235) in view of Emtage (US 2003/0113919), Kirkwood (J. Clin. Oncol. 19(9): 2370-80 (2001)) and Morton et al. ("Morton"; CA Cancer J. Clin. 46(4): 225-44 (1996)). Claims 18-21 and 39 have been cancelled; the rejections of these claims are therefore moot. Applicants respectfully maintain that the remaining rejections in this Office Action are inapplicable to the instantly pending claims.

Applicants respectfully maintain that the combined teachings of the references would not have suggested Applicants' claimed invention to those of ordinary skill in the art. There is nothing in the cited art that would have suggested to one of ordinary skill in the art that one should administer to a patient having metastatic melanoma a "composition comprising a recombinant virus encoding a melanoma-associated tumor antigen along with at least one peptide comprising an epitope of the tumor antigen such that the mammal develops a T-cell immune response against the tumor antigen" (step a) and "subsequently administering at least 10 MU/m^2/day interferon alpha 2b (IFN-α2b) as

the sole active pharmaceutical agent to the mammal for four weeks, wherein the IFN-α2b is initially administered between 1.5 and 17 months after step (a) provided there is no evidence of T cells reactive against the tumor antigen in the mammal as measured by flow cytometric assay or ELISPOT assay" (step b), "wherein, following steps (a) and (b), the mammal has no evidence of metastatic disease." The Office Action alleges that the cited references, in combination, render the previously pending claims obvious because, in part, "the claimed methods do not require any specified therapeutic efficacy" (Office Action, p. 18). As amended, instant claim 1 requires a lack of "evidence of metastatic disease" in the treated mammal. Thus, this line of reasoning is not applicable to the amended claims.

Amended claim 1 also requires that, prior to administration of interferon, "there is no evidence of circulating T cells reactive against the tumor antigen in the mammal as measured by flow cytometric assay or ELISPOT assay". Applicants acknowledge that one of ordinary skill in the art may have thought an initial immune response following vaccination to be important. However, Applicants also maintain that that skilled person would have had no reason to believe that high dose interferon should be administered after that initial immune response had subsided, as instantly claimed. Applicants, however, recognized this step as important to the success of the method of treatment as a whole. Applicants do not believe this limitation of claim 1 (and, accordingly, each of the dependent claims) is taught or in any way suggested by the cited art. It is therefore respectfully requested that these rejections be withdrawn.

B. Rejection of claims 24-26 and 36 as obvious over Paoletti in view of Emtage, Kirkwood, Aarts, and Kawakami.

Claims 24-26 and 36 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Paoletti in view of Kirkwood, Emtage, and Morton, and further in view of Kawakami (U.S. Pat. No. 5,844,075). Applicants respectfully maintain that these references cannot be combined to support a *prima facie* case of obviousness against the instantly pending claims.

Applicants' position with respect to the combination of Paoletti, Kirkwood, Emtage, and Morton disclosures were set forth in the preceding section, and are

maintained with respect to these rejections. The Office Action alleges that Kawakami teaches gp100 peptides. Applicants respectfully maintain that Kawakami cannot substitute for the deficiencies of the other cited references described above. Taken together, the cited references do not disclose or in any way suggest Applicants' instantly claimed methods. Accordingly, the reference cannot be used in combination with Paoletti, Kirkwood, Emtage, and Morton to support a proper *prima facie* case of obviousness regarding the instantly pending claims. It is therefore respectfully requested that these rejections be withdrawn.

B. Rejection of claims 24-26 and 36 as obvious over Paoletti in view of Emtage, Kirkwood, Aarts, and Kawakami.

Claims 38 and 39 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Paoletti in view of Kirkwood, Emtage, Morton as described in section (A) above, and further in view of Kuvshinoff et al. (Ann. Surg. Oncol. 4(3): 252-8 (1997)). Claim 39 has been cancelled; the rejection thereof is accordingly moot. Applicants respectfully maintain that these references cannot be combined to support a *prima facie* case of obviousness against instantly pending claim 38.

Applicants' position with respect to the combination of Paoletti, Kirkwood, Emtage, and Morton disclosures were set forth above, and are maintained with respect to these rejections as claim 38 is dependent upon claim 1. The Office Action alleges that Kuvshinoff teaches that metastatic disease may be detected using radiography. Applicants respectfully maintain that Kuvshinoff cannot substitute for the deficiencies of the other cited references described above. Taken together, the cited references do not disclose or in any way suggest Applicants' instantly claimed methods. Accordingly, the reference cannot be used in combination with Paoletti, Kirkwood, Emtage, and Morton to support a proper *prima facie* case of obviousness regarding the instantly pending claims. It is therefore respectfully requested that these rejections be withdrawn.

CONCLUSIONS

Reconsideration of this application is respectfully requested. Applicants believe the claims are in condition for allowance and respectfully request the issuance of a Notice of Allowance as soon as possible. The Examiner is encouraged to contact the undersigned if it is believe doing so would expedite prosecution of this application.

Respectfully submitted,

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